

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
6 March 2003 (06.03.2003)

PCT

(10) International Publication Number  
**WO 03/017985 A1**

(51) International Patent Classification<sup>7</sup>: **A61K 9/24**,  
31/43, 31/42

(21) International Application Number: PCT/CH02/00454

(22) International Filing Date: 20 August 2002 (20.08.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
01810825.8 23 August 2001 (23.08.2001) EP

(71) Applicant (for all designated States except US): **CIMEX**  
AG [CH/CH]; Birsweg 2, CH-4253 Liesberg (CH).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **KELBERT, Michel**  
[FR/FR]; 6, rue du Rhin, F-68730 Blotzheim (FR).

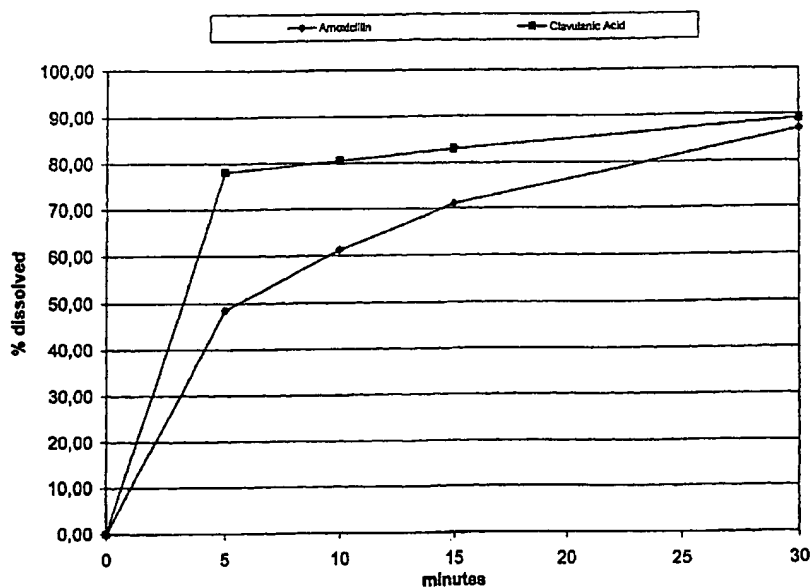
(74) Agent: **ARNOLD, Winfried, K., M.**; Brügglistrasse 9,  
CH-4104 Oberwil (CH).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **BILAYERED DISPERSIBLE TABLET FORMULATION COMPRISING AMOXYCILLIN AND CLAVULANATE IN SEPARATE LAYERS**



(57) Abstract: Pharmaceutical formulations for the manufacture of a bilayered dispersible tablet comprising in a first formulation amoxycillin together with pharmaceutically acceptable excipients and in a second formulation clavulanate together with pharmaceutically acceptable excipients, which are used for the manufacture of a bilayered dispersible tablet which is rapidly disintegrating and rapidly releasing the active ingredients into an aqueous fluid, methods for the preparation of such formulations and tablets and their use for oral treatment of bacterial infections.



WO 03/017985 A1

BILAYERED DISPERSIBLE TABLET FORMULATION COMPRISING AMOXYCILLIN AND  
CLAVULANATE IN SEPARATE LAYERS

**Field of the Invention**

This invention relates to novel pharmaceutical formulations comprising amoxycillin and clavulanic acid, which are suitable for the manufacture of oral bilayered, dispersible tablet formulations with rapid disintegrating and rapid dissolution properties. The active ingredients are readily dissolved in aqueous fluids after disintegration of the tablet.

**State of the Art**

Amoxycillin is a known beta-lactam antibiotic. Clavulanic acid is a known beta-lactamase inhibitor. Both compounds are used together in a synergistic manner in antibiotic formulations. Clavulanic acid, by inhibiting the enzyme beta-lactamase, serves to prolong the lifetime of amoxycillin in the patient by preventing early destruction thereof. In oral formulations amoxycillin is generally used in the form of its trihydrate, and clavulanic acid is generally used in the form of a pharmaceutically acceptable salt (hereinafter "clavulanate"), in particular the potassium clavulanate. For example GB 2005538 discloses formulations comprising amoxycillin trihydrate and potassium clavulanate. Such compositions are known and marketed under the trade name Augmentin®.

The Augmentin® tablet on the market is a film tablet formulation. Complete disintegration of this tablet in water at 37° C takes about 10 to 15 minutes.

For certain instances it is of advantage to provide oral pharmaceutical formulations which disintegrate very rapidly in aqueous fluids and, as a second requirement, also rapidly release the active material content in the stomach or in the intestine.

Sachets contain Augmentin® in the form of a powder, which is readily disintegrated in water and immediately forms a dispersion. Sachets have certain drawbacks and in comparison to tablets are expensive to manufacture.

Another powder form is provided in so called "dry syrup" form. The powder is provided in a sufficiently large bottle, to which prior to use the prescribed amount of water is added to give multiple variable doses as a dispersion. The desired amount of the dispersion is taken orally by the patient according to his need. Such multiple variable "dry syrup" is particularly used for children. A drawback of the "dry syrup" powder is that the clavulanate is very sensitive to hydrolysis. After addition of water and upon storage of the dispersion the activity of clavulanate may be diminished or destroyed.

Under other circumstances it is of advantage to release the active ingredient at a controlled, in particular delayed rate. The release of the active material into the stomach or intestine occurs thereby over a period of several hours after ingestion of the formulation. This allows unit doses of the formulation to be taken at widely separated intervals, for example twice daily, whilst maintaining a therapeutically effective plasma level of the active substance.

A controlled rate of release may be achieved through known layered tablets. GB 1346609 discloses three-layer tablets having two drug containing layers located one on each side of an inert disintegrable intermediate layer. US 4,122,157 discloses a controlled release nitrofurantoin tablet which comprises two adjacent layers, one being a rapid release layer, the other being a slow release layer.

Amoxycillin trihydrate and clavulanate differ substantially with respect to their solubility in water. Potassium clavulanate is freely water-soluble (about 1 part of water for 1 part of solute), whereas amoxycillin trihydrate is only slightly soluble (about 100 to 1000 parts of solvent for 1 part of solute). It is known that clavulanate is relatively sensitive to hydrolysis (maximum stability at a pH of 6.0 to 6.3), so that degradation of clavulanate may occur already in the aqueous fluid or between the relatively long period after oral administration and the contact with the aqueous gastrointestinal fluids.

According to WO 95/20946 a controlled-release tablet formulation for oral administration is disclosed comprising a first layer which includes amoxycillin and/or clavulanate, and a second layer which includes amoxycillin and/or clavulanate, provided that the overall tablet contains amoxycillin, wherein the relative rate of release of amoxycillin and/or clavulanate from the first and second layer differs. For example a first layer is disclosed to be a rapid release layer,

which releases the bulk of its active material content within a "relatively short time", for example within 1 hour, e.g. within 30 minutes after oral ingestion. The second slow release layer releases the bulk of its active material content during a relatively long period after oral ingestion or is a delayed release layer which releases the bulk of its active material content after a period of delay after oral ingestion, either in the stomach or in the intestine.

A disadvantage of the bilayered tablet formulation according to WO 95/20946 and other controlled, i.e. slow release formulations is that they are not fast enough dispersible in water which is required for certain purposes. For example the about 1.5 g film coated tablet Augmentan® (German version of Augmentin®) containing 875 mg of amoxycillin and 125 mg of potassium clavulanate, is not dispersible fast enough in water to be orally administered in the form of a solution or a dispersion. Such tablets cannot be dispersed in water shortly before oral administration. They also will not disperse fast enough in the mucosal fluid.

Oral administration in aqueous solution is, in particular, desirable for children, elderly or other patients, who cannot swallow large 1.5 g tablets. This category includes also small animal patients.

In conclusion, the known pharmaceutical formulations comprising amoxycillin and clavulanate have certain disadvantages, drawbacks and limited applicability, which can be summarized as follows:

- The known film tablets and bilayered tablets do not disintegrate fast enough in water to be useful as dispersible tablets. Some have an unwanted slow release effect.

- These tablets, in view of their size, may create difficulties in swallowing, especially for children and elderly patients.

- Conventional homogeneous tablet formulations having a high content of above 875 mg of amoxycillin and 125 mg of clavulanate do not disintegrate fast enough to give a dispersion within 1 to 3 minutes.

- Sachets contain a powder, which is not intended for direct swallowing, but must be dispersed in water.

- Only a single dosage is possible. Application of an exact part of a sachet, e. g. of the exact half thereof, is hardly possible for the patient to achieve. Devices are necessary which are usually not available to the patients.

- Sachets are furthermore expensive to manufacture.

– The powder of "dry syrup" formulations is provided in large bottles. Similar problems exist with respect to administering a defined part of the dispersion.

– The powder after dispersion in water and storing several days may lose the activity in view of the instability of clavulanic acid.

5        There exists need for an improved oral pharmaceutical formulation.

### **Object of the Invention**

It is an object of the present invention to avoid the drawbacks of formulations of prior art, and to combine their advantages in one pharmaceutical  
0        formulation. The present formulations facilitate oral administration. They can be orally administered in various manners. They may be swallowed as a whole, divided in defined smaller parts for application of defined smaller amounts of active ingredients, or rapidly dispersed in an aqueous fluid and administered for example by means of a spoon or drop by drop. Such tablet can be easily used for grown-up  
15        patients, children, babies, as well as small and large animals.

It is an object of the present invention to provide a dispersible pharmaceutical tablet formulation for oral administration comprising amoxycillin and clavulanate, which can be orally administered to children and grownup patients without providing any problems in swallowing or other throat problems.

20        The solution provided by the present invention is a bilayered dispersible tablet, which is readily disintegrated in aqueous fluids, such as water, mucosal or intestinal fluids within up to 1 or 3 minutes. The size of the majority of the particles of the dispersion is preferably smaller than 0.7 mm. The tablets may be divided, swallowed, chewed or dispersed in an aqueous fluid before oral application.

25        It is an object of the present invention to provide a dispersible bilayered tablet in which the amoxycillin and the clavulanate are separated, each one provided in a separate layer. The tablet is produced from two pharmaceutical formulations comprising the amoxycillin and the clavulanate, respectively, allowing rapid disintegration and rapid simultaneous release of the active principals in  
30        aqueous fluids.

In order to provide simultaneous rapid release of the two active ingredients the two formulations must be designed to guarantee rapid disintegration and uniformity of the particles. These goals are achieved by the careful selection of the

disintegrant, additional ingredients, and other parameters, such as form of the tablet and the hardness.

Another object is the easy and commercially advantageous and acceptable preparation of such tablet.

- 5 Another object is the use of such tablet in combating infections in a patient in need thereof.

### **Detailed Description of the Invention**

The objects of the invention are achieved by providing two pharmaceutical  
10 formulations of which one comprises an effective amount of amoxycillin and the other an effective amount of clavulanate, both active ingredients along with appropriate pharmaceutically acceptable excipients and coadjuvants, which formulations are suitable for the manufacture of a bilayered dispersible tablet.

### **15 The Pharmaceutical Formulations**

The two layers of the bilayered dispersible tablet are formed from two pharmaceutical formulations. The ingredients of the formulations have to be carefully selected to assure rapid disintegration and rapid simultaneous release of the two active ingredients in the aqueous fluid.

- 20 Besides amoxycillin and clavulanate the first and second pharmaceutical formulations comprise, independent from each other, additional pharmaceutically acceptable ingredients. These are mainly selected from disintegrants, fillers or diluents, desiccants, lubricants or flow enhancing glidants. Further ingredients may be viscosity enlarging ingredients, tablet binders, colouring agents, and optionally  
25 flavoring and/or sweetening agents.

The disintegrant is of particular importance to assure the defined rapid disintegration of the tablet in aqueous fluids. The term "disintegrant" in this description refers to an agent, which increases the surface area of the tablet in water so that the tablet rapidly disintegrates into small particles. Polymers which  
30 have a high degree of disintegration power include, inter alia, crosslinked sodium carboxymethyl-cellulose, cross-linked hydroxypropylcellulose, highmolecular weight hydroxy-propylmethylcellulose, carboxymethylamide, potassium methacrylatedivinyl-benzene copolymer, polymethylmethacrylate, cross-linked polyvinylpyrrolidone, high-molecular weight polyvinylalcohols, microcrystalline

cellulose, and the like. Examples of such polymers include Methocel K4M<sup>®</sup>, Methocel E5<sup>®</sup>, Methocel E50<sup>®</sup>, Methocel E4M<sup>®</sup>, Methocel K15M<sup>®</sup> and Methocel K100M<sup>®</sup>. An example of a suitable polymer mixture is a mixture of Methocel ES<sup>®</sup> and K4M<sup>®</sup> in the ratio of 1:1 by weight. Particular examples of disintegrants are  
5 sodium starch glycolate, e. g. Explotab<sup>®</sup>, polymeric derivatives of acrylic acid, and preferably crospovidone (an insoluble polyvinylpyrrolidone), e.g. PolyPolyplasdone<sup>®</sup> XL, or microcrystalline cellulose, e. g. Avicel<sup>®</sup>.

Sodium starch glycolate may be used in concentrations exceeding 5% by weight in relation to the total weight of the formulation, in particular about 9.5% to  
0 17%.

Polymeric derivatives of acrylic acid may be used in amounts of between about 10% to 21% of the total formulation weight.

Crospovidone may be used in a concentration of between about 4% and 16%, in particular about 4.15% in the amoxycillin formulation and about 15.5% in  
15 the clavulanate formulation of the total formulation weight.

The term "about " as used hereinbefore and hereinafter in connection with weights or other measures may be interpreted to mean plus or minus 10%.

Fillers or diluents facilitate compression of the powder and have an influence on the hardness of the tablet after compression. Such compounds  
20 comprise mannitol, microcrystalline cellulose, e. g. Avicel<sup>®</sup> PH101, in particular cellulose powder, e. g. Elcema<sup>®</sup> G 250, and silicon dioxide, e.g. Syloid<sup>®</sup> AL FP.

Fillers are used in amounts of about 5% to 10%, in particular 8.3% in the amoxycillin formulation and about 20% to 50%, in particular 39% in the clavulanate formulation of the total formulation weight.

Lubricants are excipients which reduce inter-particle friction inside the tablet and reduce the reaction forces appearing on the wall of the matrix. Lubricants are for example talcum, stearyl fumarate, polyethyleneglycol, salts of benzoic acid, such as the sodium or lithium salt, and in particular magnesium stearate. Lubricants may be used in amounts of between about 0.1% and 1%, in particular  
25 about 0.2% in the amoxycillin formulation and about 0.65% in the clavulanate formulation in relation to the total formulation weight.  
30

Further ingredients may include binders, such as Polyplasdone K29-32<sup>®</sup>, polyethylene glycol 6000, e. g. Magrocol<sup>®</sup>, compression aids, and the like.

Flavouring agents have for example the taste of a natural fruit, such as orange, lemon, apple, strawberry, vanilla, or of a herb, for example peppermint, or of broiled or fried meat, such as extracts from liver or yeast.

Sweetening agents are for example, saccharin, aspartam, cyclamate and mixtures thereof. The flavouring and sweetening agents and the amounts should be adjusted to the patient to be treated.

The pharmaceutical formulations of the invention may also include a pH modifying agent, such as a pH buffer, which may be contained in the rapid disintegrating layers. A suitable buffer is calcium hydrogen phosphate.

Colouring agents serve to give a pleasant view and/or to optically distinguish between the two formulations. Such agents are for example tartrazin (E102), chinolin yellow (E104) and yellow orange (E110)

One of the formulations may comprise a colorant agent to easily distinguish one formulation from the other and to provide uniform colour.

Suitably such a rapid release formulation may comprise around 30 - 70 % (all percentages given herein are on a weight percentage basis unless otherwise stated) e.g. 50-60% of active material content, around 10 - 30% of disintegrants, fillers, lubricants, compression aids, viscosity enlarging ingredients, tablet binders, colouring agents, viscosity enlarging ingredients, tablet binders, colouring agents, flavouring and sweetening agents, and the like.

Preferred ingredients in the amoxicillin formulation are in particular cross-povidone, cellulose powder, orange flavour, saccharine, chinolin yellow (E102), and magnesium stearate

Preferred ingredients in the clavulanate formulation are in particular crosspovidone, cellulose powder, chinolin yellow (E102) and magnesium stearate

### **The Manufacture of the Pharmaceutical Formulations**

In a further embodiment, the invention provides a method for the manufacture of the two pharmaceutical formulations described hereinabove, characterised in homogeneously mixing amoxicillin with the additional pharmaceutically acceptable excipients and coadjuvants, passing the mixture through a suitable sieve, homogeneously mixing the clavulanate with the additional pharmaceutically acceptable excipients and coadjuvants, and passing

the mixture through a suitable sieve. Amoxycillin may be used in the compacted form.

Typically the active material content (may also be amoxycillin powder), disintegrants, fillers, lubricants, viscosity enlarging ingredients, tablet binders, colouring agents, viscosity enlarging ingredients, tablet binders, colouring agents, flavouring and sweetening agents, when used, are mixed, then lubricants and compression aids are added. The complete mixture, in particular when amoxycillin powder is used, may then be compressed under high pressure in the tablet press. Roller compaction may be used to form granulates for tableting. Alternatively wet granulation may be used, isopropanol being a suitable solvent. A suitable wet granulating aid is Polyplasdone K29-32®.

Clavulanic acid and its derivatives are extremely water sensitive, potassium clavulanate being the most stable pharmaceutically acceptable derivative. Therefore formulations containing derivatives of clavulanic acid, such as potassium clavulanate, should be made up in dry conditions, preferably at 20% relative humidity or less at 20° C, and the ingredients of the formulation should be pre-dried where appropriate. Formulations of the invention including derivatives of clavulanic acid should be stored in containers which are sealed against the ingress of atmospheric moisture.

In particular the active ingredients, amoxycillin powder or clavulanate, fillers and diluents, e. g. cellulose powder, which may contain the colouring agent, or mannitol, release controlling agents (e. g. Methocel®), and disintegrants, e. g. crospovidone (e. g. Polyplestone®) and binders (e. g. Polyplasdone K29-32®) are mixed during 5 minutes in a Stefan® Mixer. Lubricants (e. g. talc, Mg-stearate) and colloidal silicon dioxide (e. g. Syloid ALFP®) are added, and mixing is continued for another minute. The complete mixture is slugged on a Fette® tablet press (briquetting step), followed by size reduction and passing through an oscillatory 1 mm sieve (Frewitt®). If the flow properties are unsatisfactory, the briquetting step is repeated.

This granulate possesses good flow properties. In some cases, where the bulk density is rather low, a densifying step (pre-tableting and sieving as in the briquetting method) is still required in order to achieve the nominal weight of a particular layer.

Coating particles and granules with Eudragit<sup>®</sup>L is performed in a similar manner. A solution of Eudragit<sup>®</sup> in isopropanol is mixed with the active ingredients or with a granulate (without talc and Mg-stearate) prepared in the aforementioned wet granulation manner. The wet cake is pressed through a 0.5 mm sieve, the  
5 mixing is repeated and followed by sieving through a 2 mm sieve.

After drying at 40° C the dried material is passed through a 1 mm sieve. The treatment with Eudragit<sup>®</sup>, sieving and drying is repeated until the nominal amount of Eudragit L<sup>®</sup> according to the recipe is contained within the granulate. Then Mg-stearate and talc are added and mixed.

10 Other coating work with Eudragit L<sup>®</sup> involves the use of a fluid bed granulator. The active ingredients are spray-coated with an isopropanolic solution of Eudragit L<sup>®</sup> in a Glatt fluid bed granulator to 20% Eudragit L<sup>®</sup> of the weight of the active ingredients. Samples are taken at the 5, 10, 15 and 20% Eudragit<sup>®</sup> weight level. In addition, a granulate of active ingredients with Methocels<sup>®</sup> is  
15 prepared in the Glatt employing an isopropanolic solution of Plasdone K-29-32. This granulate is then spray-coated with Eudragit L<sup>®</sup> on the Glatt.

### **The Use of the Pharmaceutical Formulations**

The invention further provides a method of use of a formulation as described  
20 above, in the manufacture of a medicament for the treatment of bacterial infections.

The medicament is in particular the bilayered dispersible tablet described herein. The two layers are formed by use of the two pharmaceutical formulations.

### **25 The Bilayered Dispersible Tablet**

The invention furthermore concerns a bilayered dispersible pharmaceutical tablet for oral administration comprising as pharmaceutically active ingredients in a first layer amoxycillin and in a second layer clavulanate, which is readily dispersible in an aqueous fluid, in that both layers are rapidly disintegrating and  
30 rapidly and simultaneously releasing the active ingredients in an aqueous fluid.

By the term "bilayered dispersible pharmaceutical tablet" is to be understood a solid preparation containing two single doses of two pharmaceutically active ingredients, each in one of the two layers. The term

"dispersible" means, the tablet is dispersible within 3 minutes in an aqueous fluid before administration, resulting in a homogeneous dispersion.

Hereinbefore and hereinafter the terms "first" and "second" layer may also be read "one" and "the other" layer, and vice versa.

5       The bilayered tablet formulation comprises preferably amoxycillin trihydrate and potassium clavulanate in pharmaceutically effective amounts. The overall weight ratio of amoxycillin : clavulanate (expressed as the free acid equivalent) may vary between broad limits, for example between about 30 : 1 to 1 : 1. Suitably the ratio may be between about 8 : 1 to 1 : 1, for example between 7 : 1 to 1 : 1,  
10       preferably about 7 : 1 or 8 : 1.

      The tablet formulations of the invention may contain up to the maximum permitted daily dose of amoxycillin and clavulanate per unit dose. The formulations may contain for example around 875 mg of amoxycillin and around 125 mg of clavulanate. Suitable unit dose tablets of the invention may contain the following  
15       nominal weights (mg) of amoxycillin : clavulanate (expressed as free acid equivalent): ratio 7:1: 875:125; 500:71.428; or 250:35.71; ratio 8:1: 875:109.375; 500:62.5; or 250:31.35; or ratio 4:1: 40:10; 200:50; or 400:100.

      Small dose for children, babies or small animals have a weight ratio of amoxycillin : clavulanate from 4 : 1 to 14 : 1, and the weights (mg) may be about  
20       40:10, e.g. also for cats; 200:50, e.g. for small dogs, or 400:100 large dogs.

      Large animals, such as horses, cows, pigs and the like need higher dosages, which can be achieved by application of more than one tablet.

      In particular the first layer of the present tablet formulation comprises about 875 mg of amoxycillin trihydrate, and the second layer comprises about 125 mg or  
25       109.375 mg of potassium clavulanate.

      Preferably bilayered dispersible tablets according to the invention are those described in the Examples. They comprise in the first layer 1027.00 mg of amoxycillin trihydrate, 100.00 mg of cellulose powder (e. g. ELCEMA G 250<sup>®</sup>) containing about 0.19 mg of chinolin yellow (E104), 50.00 mg of crospovidone (e.  
30       g. Polyplasdone XL<sup>®</sup>), 20.00 mg of orange flavour, 5.00 mg of saccharine and 2.50 mg of magnesium stearate, and in the second layer 149.70 mg of potassium clavulanate, 150.00 mg of cellulose powder (e. g. ELCEMA G 250<sup>®</sup>) containing about 0.75 mg of chinolin yellow (E104), 60.00 mg of crosspovidone (e. g.

Polyplasdone XL<sup>®</sup>), 25. mg of silicium dioxide (e. g. Syloid AL FP<sup>®</sup>) and 2.50 mg of magnesium stearate,

The hardness of the bilayered dispersible tablet is about 100 to 300 Newton, preferable about 180 Newton.

- 5        The form of the tablets is one of the usual round, spherical, block or oblong forms. If intended for swallowing the oblong form is preferred.

### **The Manufacture of the Bilayered Dispersible Tablet**

- 10        In a further embodiment, the present invention provides a method for the preparation of a bilayered dispersible tablet, characterised by pressing in a tablet matrix one pharmaceutical formulation of the invention on top of the other.

Suitably the tablet formulations of the invention may be formed by known compression tableting techniques, for example using a known multi-layer tableting press. Suitably a dry densification process may be used, e.g. briquetting.

- 15        The form of the matrix is the one for achieving the desired form of the tablet.

The manufacture of the bilayered tablets may involve granulation of the pharmaceutical formulation prior to pressing. Preferred is the dry granulation, i. e. without prior wet granulation.

- 20        The pressure applied is between about 15 to 50 KN, preferably about 25 KN. The pressure for the first/amoxycillin layer may be lower than the one for the second/clavulanate layer. The resulting hardness is about 100 to 300 Newton, preferable about 180 Newton.

- 25        Tablets may have any conventional structure, e.g. by using an oval matrix and a biconvex punch 21 x 10 mm, having a rapid-disintegrating first and second layer.

### **The Use of the Bilayered Dispersible Tablet**

- 30        In a further embodiment, the invention provides the use of the bilayered dispersible tablet formulation as an active therapeutic in the treatment of bacterial infections of a host in need thereof.

The bilayered dispersible tablet of the invention may be swallowed, chewed or, before use, dispersed in water or another aqueous fluid of room temperature, e.g. between 15 to 25<sup>0</sup> C, and administered orally in the form of a dispersion. The amount of fluid is not critical. In general an amount for easy swallowing is taken.

Children and babies are conveniently treated with a disintegrated dispersion of a tablet in water, a syrup, or a fruit juice, a tea, or any other pharmaceutically acceptable water containing fluid, eventually spoon by spoon. For animals the tablets may be added to the food, or disintegrated in water and this form added to the food or injected into the mouth by means of a pipette.

For oral administration the amount of the aqueous fluid for one tablet is from e.g. 50 to 100 ml to achieve a concentration of the amoxycillin of about 0.041 % to 2 %, preferably about 0.04 % to 0.875 %, and of clavulanate of about 0.01% to 0.3%, preferably 0.01 % to 0.125 %, +/- 10 %.

- ) The tablet formulations of this invention immediately and simultaneously provide high plasma levels of amoxycillin and clavulanate after oral administration.

The bilayered dispersible tablet disintegrates in water of room temperature, e.g. of between 15 and 25<sup>0</sup> C, below 3 minutes, e. g. between about 0.3 and 1 minute, or about 0.5 minutes, and particularly below 1 minute.

- 5 Within 5 minutes the bilayered tablet formulation according to the invention releases in water of 37<sup>0</sup> C about 40 % to 60 %, or an average of about 48.6 %, of the amoxycillin trihydrate , and about 80 % to 95 % or an average of about 78 % of the potassium clavulanate.

- 10 Within 30 minutes about 87 % of the amoxycillin trihydrate and about 89 % of the potassium clavulanate is released in water of 37<sup>0</sup> C.

- 25 In a further embodiment the invention provides the use of the bilayered dispersible tablet formulation for preparation of a pharmaceutical package for the treatment of bacterial infections of a host in need thereof. A pharmaceutical package may be any of a suitable package in this field, such as a filled up glass bottle, optionally equipped with a desiccant, or a suitable blister package.

- 30 In a further embodiment, the invention provides a method of treatment of bacterial infections of a host in need thereof, comprising administering to the said host a bilayered dispersible tablet formulation comprising as pharmaceutically active ingredients in a first layer amoxycillin and in a second layer clavulanate, characterised in that both layers are rapidly disintegrating and releasing the active ingredients into an aqueous fluid.

The invention also provides a method for the manufacture of a tablet formulation as described above comprising the steps of forming said first and second layers, and any barrier layers and coating layer(s) which may be present.

The invention further provides a method of treatment of bacterial infections in humans or animals which comprises the administration of a therapeutically effective amount of active material content included in a tablet formulation as described herein.

Following is a short description of the accompanying drawings:

Fig 1 shows the percentage dissolution vs. time of amoxycillin and clavulanic acid of six individual tablets prepared according to Example 1 determined in water at 37° C by applying the paddle method described in European Pharmacopoeia 1997, 3<sup>rd</sup> Ed., page 128.

) Fig. 2 shows the percentage dissolution vs. time of amoxycillin of six individual tablets prepared according to Example 1 in water at 37° C using the paddle method as described under Fig. 1

Fig. 3. shows the percentage dissolution vs. time of potassium clavulanate of six individual tablets prepared according to Example 1 in water at 37° C by  
5 applying the paddle method as described under Fig. 1

The following examples serve to further characterise the invention, however, should not be construed as a limitation thereof.

10 **Example 1. Preparation of bilayered dispersible tablets with 1027 mg of amoxicillin trihydrate and 149.7 mg of potassium clavulanate (7:1)**

The ingredients for the two formulations of one tablet are given in the following Tables 1 and 2.

**Table 1: I. Amoxycillin containing formulation for one tablet layer**

	Compounds	mg/Tablet
1	amoxycillin trihydrate, compacted	1027.00
2	cellulose powder (ELCEMA G 250 <sup>®</sup> ), containing 0.19 mg of chinolin yellow (E104)	100.19
3	crosspovidone (Polyplasdone XL <sup>®</sup> )	50.00
4	orange flavour	20.00
5	saccharine	5.00
6	magnesium stearate	2.50
<b>Total weight of the amoxycillin formulation</b>		<b>1204.69</b>

The ingredients 1 – 5 of the amoxicillin formulation I are passed through a 1.0 mm oscillatory sieve and for 10 minutes at 15 rpm carefully mixed. The lubricant ingredient 6 is added and mixing continued for 3 minutes at 15 rpm.

**Table 2: II. Clavulanate containing formulation for the other tablet layer**

	Compounds	mg/Tablet
7	potassium clavulanate	149.70
8	cellulose powder (ELCEMA G 250 <sup>®</sup> ) containing 0.75 mg of chinolin yellow (E104)	150.75
9	crosspovidone ( Polyplasdone XL <sup>®</sup> )	60.00
10	silicon dioxide (Syloid AL FP)	25.00
11	magnesium stearate	2.50
<b>Total weight of clavulanate formulation</b>		<b>387.95</b>

The ingredients 7 – 10 of the clavulanate formulation II are passed through a 1.0 mm oscillatory sieve and carefully mixed for 10 minutes at 15 rpm . The lubricant ingredient 11 is added and mixing continued for 3 minutes at 15 rpm.

The complete mixture is slugged on a rotary tablet press or alternatively compacted with a Bepex<sup>®</sup> compactor at a pressure of about 45 KN, followed by size reduction with an oscillatory 1.0 mm sieve (Frewitt<sup>®</sup>). The mixture is kept below 20% room humidity and at 20<sup>0</sup> C

15

#### **Preparation of the bilayered dispersible tablet**

The amoxicillin formulation I is first filled into an oblong tablet matrix of 20.7 x 10.8 mm and pressed using an oblong punch with 1204.69 mg. The clavulanat formulation II is added and pressed with 387.95 mg. A bilayered dispersible tablet with a total weight of 1592.64 mg results.

20

For the production of 300 000 tablets aliquots of the numbers in grams are used.

The tablet is 8.8 mm high and easily dividable, in particular when one or two break marks are present. The hardness is about 150 – 200 N. The disintegrating time is below 1 minute in water at 20° C.

### Example 2. Disintegration Report

Six randomly selected tablets of Example 1 were tested in the basket apparatus at 20° C according to European Pharmacopeia, 1997, 3<sup>rd</sup>. Edition, page 127, and compared in a parallel test with randomly selected six commercially available coated Augmentan® (Beecham Germany) tablets containing 1004.31 mg of Amoxycillin trihydrate and 148.83 mg of potassium clavulanate. The results are shown in Table 3.

Table 3

Disintegrating time in minutes at 20° C	
Augmentan®	Tablets of Example 1
14.2	0.38
14.4	0.4
15.1	0.4
15.4	0.44
15.5	0.53
16.5	1.0

The comparative test results indicate that the disintegrating time of Augmentan® is too high for use as a dispersible tablet, whereas the disintegrating time for the tablet according to the invention fulfills the requirements for a dispersible tablet.

### Example 3. Dissolution Report

Six randomly selected bilayered dispersible tablets of Example 1 were tested in a paddle apparatus according to European Pharmacopoeia 1997, page 128. One tablet was put into 900 ml of water of 37° C. Stirring was performed with 75 rpm. The content of active ingredient in the water was determined by HPLC analysis immediately, and after 5, 10, 15 and 30 minutes. The results are compiled in the following tables.

**Table 4: Amoxycillin**

Minutes	Tablet No. - % dissolved						Average	Srel
	1	2	3	4	5	6		
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	45.28	51.22	50.46	53.62	47.69	43.50	48.63	7.88
10	57.88	68.29	61.89	58.06	64.47	57.18	61.30	7.24
15	67.50	79.40	70.28	67.62	74.69	66.68	71.03	7.10
30	83.37	95.38	83.25	84.96	91.46	83.79	87.04	5.90

**Table 5: Clavulanate**

Minutes	Tablet No. - % dissolved						Average	Srel
	1	2	3	4	5	6		
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	94.43	59.91	90.90	80.85	58.51	84.47	78.18	19.76
10	94.05	67.22	90.65	81.74	64.79	84.88	80.55	15.01
15	94.32	74.42	90.54	83.33	70.24	85.78	83.11	11.15
30	94.22	88.81	90.44	87.09	85.83	89.13	89.25	3.27

5 Srel = relative standard deviation

The results of the tables 4 and 5 are graphically shown in Figures 1, 2, and 3, respectively.

Fig. 1 shows the average dissolution of six tablets of amoxycillin and clavulanate of Table 4 and 5 from 0 to 30 minutes .

10 Fig. 2 shows the individual dissolution profiles of the six tablets of Table 4 with respect to amoxycillin.

Fig. 3 shows the individual dissolution profiles of the six tablets of Table 5 with respect to clavulanate.

15 **Example 4. Preparation of bilayered dispersible tablets with 1027 mg of amoxicillin trihydrate and 130.89 mg of potassium clavulanate (8:1)**

The ingredients of the two formulations are given in Tables 6 and 7.

**Table 6: I. Amoxycillin containing formulation for one tablet layer**

	Compounds	mg/Tablet
1	amoxycillin trihydrate, compacted	1027.00
2	cellulose powder (ELCEMA G 250 <sup>®</sup> ), containing 0.19 mg of chinolin yellow (E104)	100.19
3	crosspovidone (Polyplasdone XL <sup>®</sup> )	50.00
4	orange flavour	20.00
5	saccharine	5.00
6	magnesium stearate	2.50
<b>Total weight of the amoxycillin formulation</b>		<b>1204.69</b>

**Table 6: II. Clavulanate containing formulation for the other tablet layer**

	Compounds	mg/Tablet
7	potassium clavulanate	130.98
8	cellulose powder (ELCEMA G 250 <sup>®</sup> ) containing 0.75 mg of chinolin yellow (E104)	131.25
9	crosspovidone ( Polyplasdone XL <sup>®</sup> )	52.50
10	silicon dioxide (Syloid AL FP)	21.875
11	magnesium stearate	2.18
<b>Total weight of the clavulanate formulation</b>		<b>339.44</b>

5        The manufacture of the two formulations and the final tablet is the same as described in Example 1. The final tablet has a weight of 1544.13 mg.

Similar results are obtained for disintegration and dissolution as in Example 2 and 3.

10

15

**Claims**

1. A first pharmaceutical formulation comprising a therapeutically effective amount of amoxycillin and a second pharmaceutical formulation comprising a therapeutically effective amount of clavulanate, both active ingredients along with appropriate pharmaceutically acceptable excipients and coadjuvants including a disintegrant, which formulations are suitable for the manufacture of a bilayered dispersible tablet.
2. A pharmaceutical formulation according to claim 1, wherein said appropriate excipients and coadjuvants comprise also desiccants, lubricants, sweeteners and  
flavourings.
3. A pharmaceutical formulation according to claims 1 or 2, wherein amoxycillin is present in form of the trihydrate.
4. A pharmaceutical formulation according to claims 1 or 2, wherein clavulanate is present in form of potassium clavulanate.
5. A first and a second pharmaceutical formulation according to claims 1-4, wherein in combination the ratio of amoxycillin trihydrate and potassium clavulanate is between about 4 : 1 to 14 : 1.
6. A first and a second pharmaceutical formulation according to claims 1-5, wherein in combination the ratio of amoxycillin trihydrate and potassium clavulanate is about 7 : 1 or 8 : 1.
7. A first and a second pharmaceutical formulation according to claims 1-6, wherein the first comprises about 875 mg of amoxycillin trihydrate and the second about 125 mg of potassium clavulanate.
8. A first and a second pharmaceutical formulation according to claims 1-6,  
wherein the first comprises about 875 mg of amoxycillin trihydrate and the second about 109.375 mg of potassium clavulanate.
9. A first and a second pharmaceutical formulation according to claims 1-8, comprising additional pharmaceutically acceptable ingredients, selected from disintegrants, viscosity enlarging ingredients, fillers, desiccants, lubricants, tablet binders and optionally colouring, flavoring and/or sweetening agents.
10. A first and a second pharmaceutical formulation according to claims 1-9, comprising additional pharmaceutically acceptable ingredients, selected from crosspovidone, cellulose powder, silicon dioxide and magnesium stearate, and optionally, colouring, flavoring and sweetening agents.

11. A first pharmaceutical formulation according to claims 1-10, comprising 1027.00 mg of amoxycillin trihydrate, 100.00 mg of cellulose powder (e. g. ELCEMA G 250®) with admixed 0.19 mg of chinolin yellow, 50.00 mg of croscopovidone (e. g. Polyplasdone XL®), 20.00 mg of orange flavor, 5.00 mg of saccharine and 2.50 mg of magnesium stearate.
12. A second pharmaceutical formulation according to claims 1-10, comprising 149.70 mg of potassium clavulanate, 150.00 mg of cellulose powder (e. g. ELCEMA G 250®) with admixed 0.75 mg of chinolin yellow, 60.00 mg of croscopovidone (e. g. Polyplasdone XL®), 25 mg of silicon dioxide (e. g. Syloid ) ALFP®) and 2.50 mg of magnesium stearate,
13. A first and a second pharmaceutical formulation according to claims 1-12, of which the tablet manufactured thereof is disintegrating in aqueous fluids of room temperature within about 0.4 -1 minute.
14. A first and a second pharmaceutical formulation according to claims 1-13, of which the tablet manufactured thereof is disintegrating in aqueous fluids of room temperature within 1 minute.
15. A first and a second pharmaceutical formulation according to claims 1-14, of which the tablet manufactured thereof is disintegrated in an aqueous beverage selected from water, fruit juice, syrup, and the like, and administered orally.
16. A first and a second pharmaceutical formulation according to claims 1-15, of which the tablet manufactured thereof is disintegrated in water and about 50 % of the amoxycillin trihydrate is dissolved in water of 37°C within 5 minutes.
17. A first and a second pharmaceutical formulation according to claims 1-16, of which the tablet manufactured thereof is disintegrated in water and about 87% of the amoxycillin trihydrate is dissolved in water of 37°C within 30 minutes.
18. A first and a second pharmaceutical formulation according to claims 1-17, of which the tablet manufactured thereof is disintegrated in water and about 78 % of the potassium clavulanate is dissolved in water of 37°C within about 5 minutes.
19. A first and a second pharmaceutical formulation according to claims 1-18, of which the tablet manufactured thereof is disintegrated in water and about 89% of the potassium clavulanate is dissolved in water of 37°C within about 30 minutes.
20. A method for the manufacture of the two pharmaceutical formulations as set forth in claims 1-19, characterised in homogeneously mixing amoxycillin with the additional pharmaceutically acceptable excipients and coadjuvants, passing the

mixture through a suitable sieve, homogeneously mixing the clavulanate with the additional pharmaceutically acceptable excipients and coadjuvants, passing the mixture through a suitable sieve

21. A method of use of a formulation as set forth in any one of claims 1-19, for the manufacture of a medicament for the treatment of bacterial infections.

22. A method of use according to claim 21, wherein the medicament is the bilayered dispersible tablet.

23. A bilayered dispersible pharmaceutical tablet for oral administration comprising as pharmaceutically active ingredients in a first layer amoxycillin and in a second layer clavulanate, which is readily dispersible in an aqueous fluid in that both layers are rapidly disintegrating and rapidly releasing the active ingredients into an aqueous fluid.

24. A bilayered dispersible pharmaceutical tablet according to claim 23, comprising a first and a second pharmaceutical formulation as set forth in anyone of claims 1-19.

25. A bilayered dispersible pharmaceutical tablet according to claim 23-24, having a hardness of about 100 to 300 Newton, preferable about 180 Newton.

26. A method for the manufacture of a bilayered dispersible tablet, characterised by pressing in a tablet matrix one pharmaceutical formulation as set forth in anyone of Claims 1-19 on top of the other.

27. A method for the manufacture of a bilayered, dispersible tablet comprising the steps of forming a first and second layer by means of a first and a second pharmaceutical formulation according to any one of claims 1-19.

28. Use of the bilayered dispersible tablet formulation as set forth in claim 23-25 as an active therapeutic in the treatment of bacterial infections of a host in need thereof.

29. A method of treatment of bacterial infections of a host in need thereof, comprising administering to said host a pharmaceutical tablet according to claims 23-25.

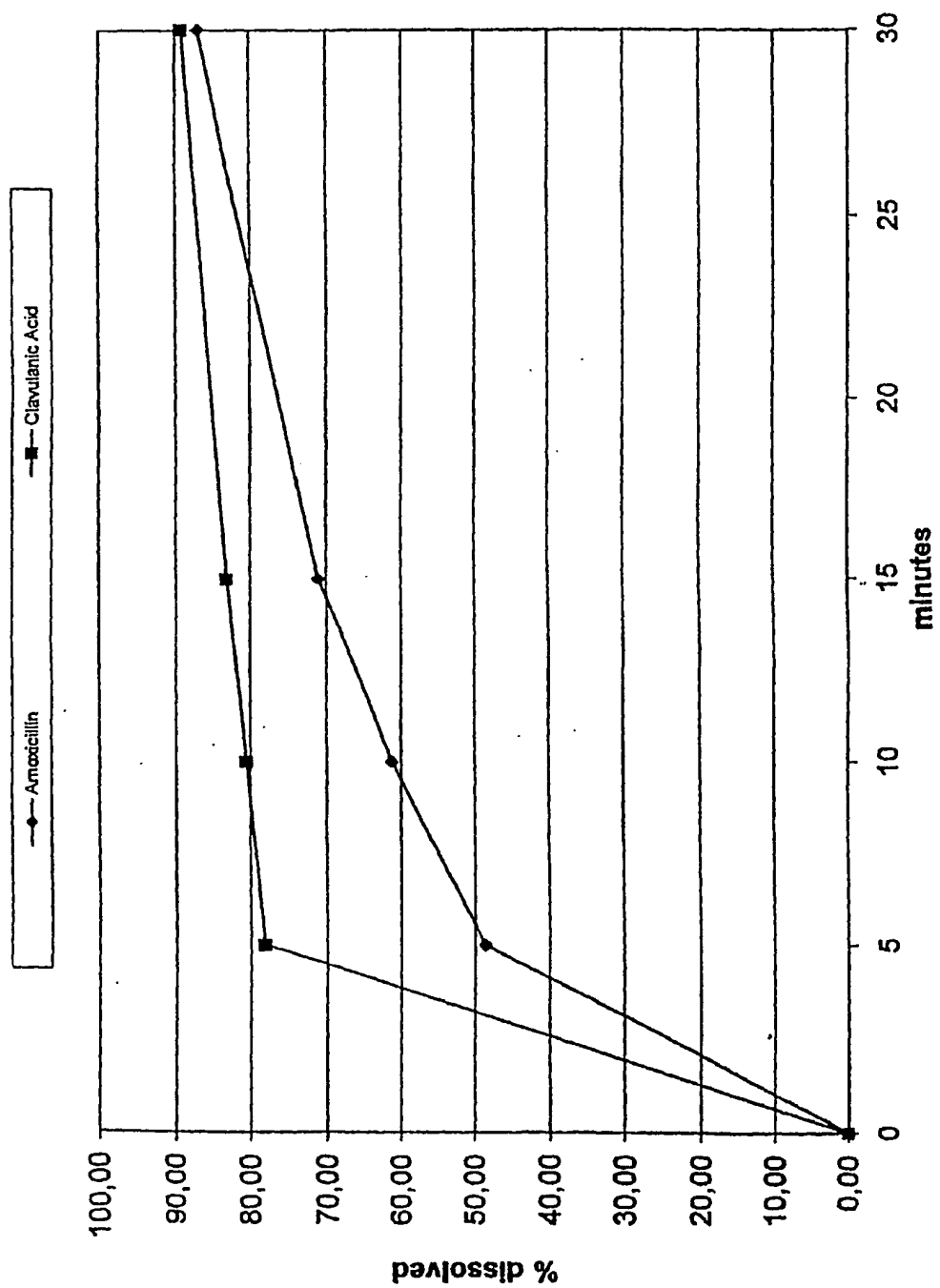


Fig. 1

### Dissolution of Amoxicillin – Individual Profiles

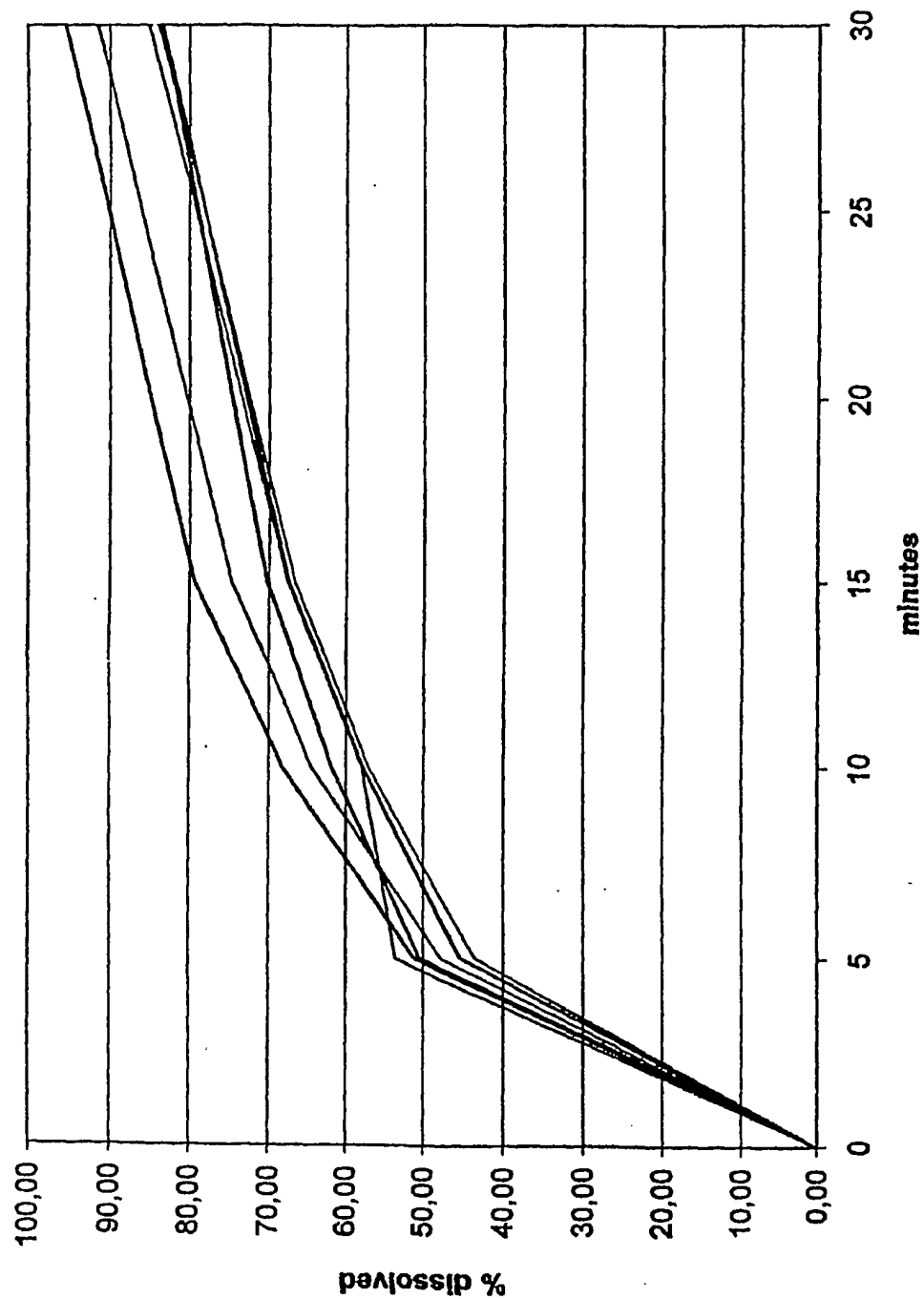


Fig. 2

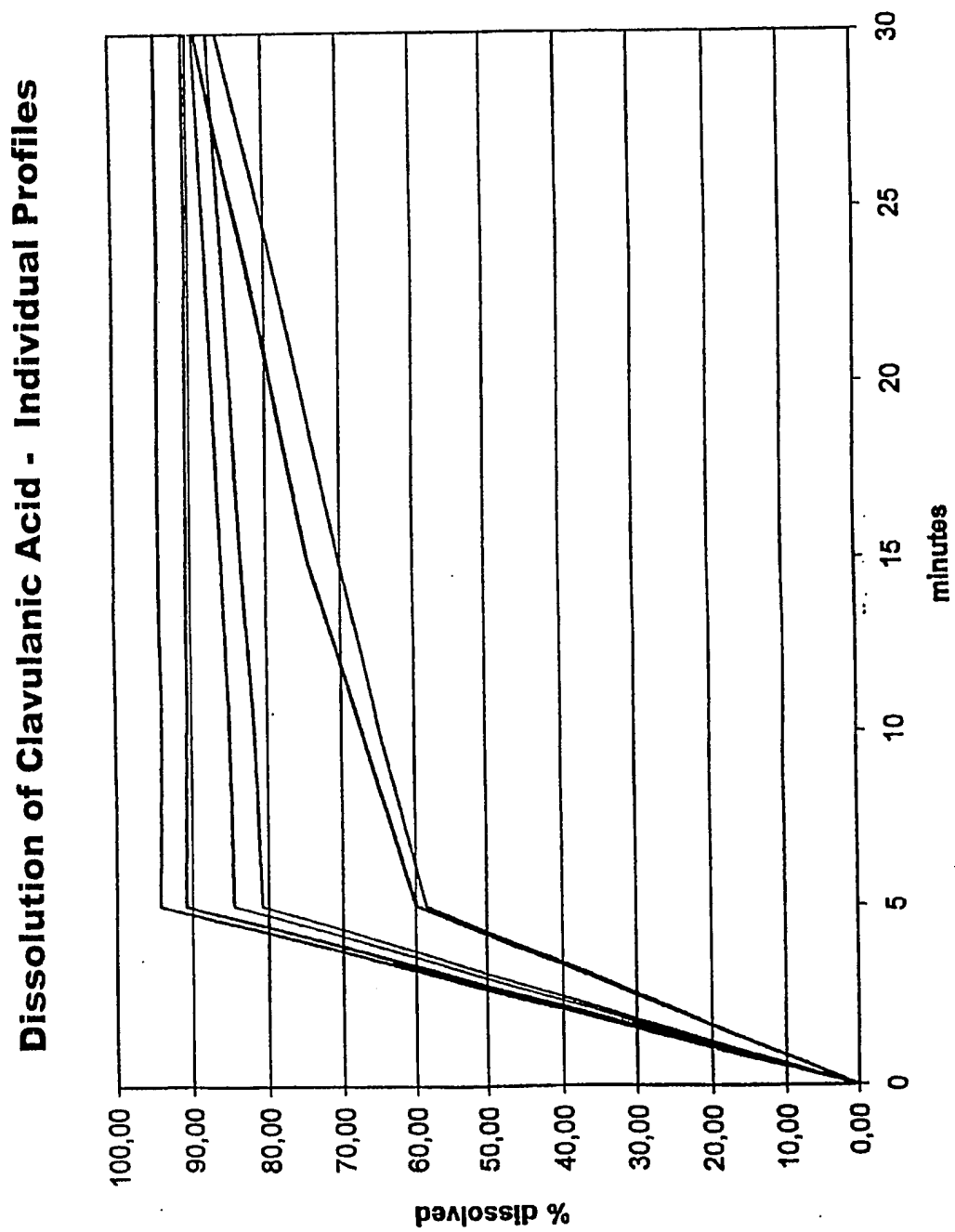


Fig. 3

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/CH 02/00454

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/24 A61K31/43 A61K31/42

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 05305 A (GRIBBON ENDA MARTIN ;MARTYN GLEN PATRICK (GB); QUADRANT HOLDINGS C) 12 February 1998 (1998-02-12) example 10 combined with examples 3-5	1-4, 9, 10, 13-29
Y	page 1, line 1-10; page 5, line 11-12; page 5, line 35 - page 6, line 4	1-29
X	WO 95 20946 A (SMITHKLINE BEECHAM PLC ;EBBERS WALTER F W (CH); ZIMMER ROBERT H (C) 10 August 1995 (1995-08-10) cited in the application examples 2-11	1-6, 9, 10, 13-29

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

15 October 2002

Date of mailing of the international search report

22/10/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Borst, M

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/CH 02/00454

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 01114 A (DIJKGRAAF BERNARDUS LEONARDUS ;MUEHLENBRUCH AART (NL); YAMANOUCI) 15 January 1998 (1998-01-15)	1-29
Y	page 1, line 1-30; page 4, line 13 - page 5, line 3; page 9, line 1-8; examples 4-15	1-29
Y	page 7, line 5-6; page 8, line 1-6 and 24-31	1-29
Y	--- EP 0 281 200 A (GIST BROCADES NV) 7 September 1988 (1988-09-07) page 2, line 1-4, 17-19; page 3, line 11-27; page 4, line 17-19; examples 3, 4 -----	1-29

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/CH 02/00454**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 15, 28, 29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition (Rule 39.1(iv) PCT).
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CH 02/00454

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9805305	A	12-02-1998	AU 3777597 A	25-02-1998
			EP 0917459 A1	26-05-1999
			WO 9805305 A1	12-02-1998
			JP 2000515538 T	21-11-2000
			US 6194001 B1	27-02-2001
WO 9520946	A	10-08-1995	DE 69521987 D1	06-09-2001
			DE 69521987 T2	04-04-2002
			DE 69526984 D1	11-07-2002
			WO 9520946 A1	10-08-1995
			EP 0742712 A1	20-11-1996
			EP 1025841 A1	09-08-2000
			JP 9509412 T	22-09-1997
WO 9801114	A	15-01-1998	AU 731276 B2	29-03-2001
			AU 3342197 A	02-02-1998
			BG 103047 A	30-07-1999
			BR 9710181 A	10-08-1999
			CZ 9900006 A3	14-04-1999
			WO 9801114 A1	15-01-1998
			EP 0910344 A1	28-04-1999
			HU 9903308 A2	28-03-2000
			JP 2000513727 T	17-10-2000
			NO 986157 A	01-02-1999
			NZ 333247 A	28-07-2000
			PL 330958 A1	21-06-1999
			SK 176798 A3	10-04-2000
			TR 9802762 T2	22-03-1999
			US 5837292 A	17-11-1998
			ZA 9705848 A	12-04-1999
EP 0281200	A	07-09-1988	AT 100317 T	15-02-1994
			AU 603870 B2	29-11-1990
			AU 1252088 A	01-09-1988
			CA 1338467 A1	23-07-1996
			CN 88101104 A ,B	21-12-1988
			DE 3887179 D1	03-03-1994
			DE 3887179 T2	16-06-1994
			DK 108888 A	03-09-1988
			EP 0281200 A1	07-09-1988
			ES 2061623 T3	16-12-1994
			FI 880928 A ,B,	03-09-1988
			IE 70907 B1	15-01-1997
			IL 85594 A	15-11-1992
			JP 63301820 A	08-12-1988
			KR 9609182 B1	16-07-1996
			NO 880904 A ,B,	05-09-1988
			NZ 223711 A	29-08-1989
			PT 86870 A ,B	01-04-1988
			US 4950484 A	21-08-1990